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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,962	NI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-47* is/are pending in the application.

4a) Of the above claim(s) *44,46 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *31-47* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/8/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Invention I, species Mab163-93 in the reply filed on 12/27/2004 is acknowledged.

Claims 44 and 46-47 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/27/2004.

Claim Objections

The claims are objected to because the facsimile transmission caused deletion of numerous vowels. Applicants are required to submit a clean copy of the claims with the response to this Office Action. If the claims are amended, the submission of claims reflecting the amendments in proper format will suffice (i.e. only one copy of the claims need be submitted).

Claim 35 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The method by which the antibody was made does not further limit (in this case) the claimed antibody.

Claim 41 is objected to for reciting a non-elected species. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The enablement of claim(s) 39 and 41 requires availability of the specific hybridomas or antibodies claimed therein. This determination has been made because said hybridomas and antibodies are not fully disclosed nor have they been shown to be publicly known and freely available. Accordingly, it is deemed that a deposit these hybridomas should have been made in accordance with MPEP Chapter 2400 and 37 C.F.R.§§1.801-1.809. Applicant is advised that the Patent Office accepts Budapest approved deposits, as long as assurance is provided that the deposited material will be made irrevocably available with no restrictions upon issuance of a patent. See MPEP Chapter 2400 at 2414.01.

The deposit statement at page 5 is noted, but is not in compliance with the requirement, as there is no accession number given, nor are the date or terms of deposit stated.

Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 is drawn to an antibody that "binds the same epitope" as monoclonal antibody 163-93. While monoclonal antibody 163-93 is described in the specification as binding to and being an agonist of G-CSF receptor, there is no written description in the specification regarding to what *epitope* the antibody binds. Epitopes can be small portions of a protein, and can be comprised of non-contiguous portions of a protein that are in proximity when the protein

assumes its three dimensional conformation. In the absence of any written description of the epitope to which monoclonal antibody 163-93 binds, there is not sufficient written description of any other antibodies that bind to the same epitope.

An epitope, or the site on the protein to which the antibody bind, can involve 15-20 amino acid residues. As stated by Kaveri in "Antibody Engineering Protocols", S. Paul, ed., "An epitope in polypeptide antigens is not necessarily contiguous in the primary linear sequence. The shape of the epitope is often established by the folding of the protein, e.g., by juxtaposition of two distinct chains of polypeptides.". Further, mere inhibition of binding of one antibody by another is *not* evidence that the two antibodies actually bind to the same epitope, as antibodies are large proteins that can sterically inhibit binding of another antibody in *proximity* to the epitope. Accordingly, although the specification provides an adequate written description of monoclonal antibody163-93, a description of the antibody itself is *not* a description of the epitope to which the antibody binds, and the specification fails to support claims to antibodies that bind to the same epitope as does monoclonal antibody163-93.

Claim 43 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising SEQ ID NO: 15-20 as the CDRs, does not reasonably provide enablement for an antibody that is a G-CSF agonist and comprises 'one or more' of said CDR's. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a

given antibody, each of which consists of three CDRs that provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity that is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. The stated of the art is that it is recognized that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979), and that the nature of the changes is not predictable. Rudikoff et al. teach that the alteration of a single amino acid in the CDR of an antibody resulted in the loss of antigen-binding function. Therefore, the art teaches that it is not predictable, and in fact, unlikely, that antibodies as defined by the claims which contain less than the full complement of CDRs from the heavy and light chain variable regions (set forth as SEQ ID NOs:15-20) of the antibodies would have the required binding function. Further, the presence of a single CDR region does not confer specificity to an antibody. The antibody's binding specificity is a function of all *six* CDR regions, as well as elements of the antibody framework. The organism has a limited (but fairly large) number of CDR sequences that are recombined to produce antibody diversity. As such, the same CDR may be used in multiple different antibodies, and, in combination with different permutations of the other five CDRs, produce antibodies of vastly different specificity. As evidence of this, see the attached sequence search results (which are only a portion of the search results obtained), in which it can be seen that antibodies that comprise the CDR having SEQ ID NO: 15 of this application have been reported to bind erb-B2, Factor IX, EGP-1 glycoprotein, myelin associated glycoprotein, NCA90, NCA95, stress protein peptide complexes and VEGF, among many others. Thus, the Examiner finds that specifying that only a single CDR region of the disclosed monoclonal antibody163-93 is not sufficient to confer specificity, in view of the art, namely Rudikoff, and the numerous sequence 'hits' that show antibodies with vastly varying specificities that comprise SEQ ID NO: 15. The specification provides no direction or guidance regarding how to produce

antibodies as broadly defined by the claims. While it would not constitute undue experimentation to find additional antibodies that function as agonists of the human G-CSF receptor (see art rejections, below), claim 43 requires that "one or more" of the CDR's be as found for monoclonal antibody 163-95. It would require undue experimentation either to randomly generate antibodies with the desired binding characteristics and then clone and sequence a sufficient number so as to discover one that uses one or more of the same CDRs as monoclonal antibody 163-95, or alternatively, to engineer an antibody that uses one or more of the same CDRs as monoclonal antibody 163-95 via genetic engineering techniques, in view of the teachings cited above. Accordingly, the Examiner concludes that undue experimentation would be required to produce the invention commensurate with the scope of the claims.

Claims 31-33, 37, 38, 40 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for G-CSF agonist antibodies that bind to the extracellular portion of G-CSF receptor, provides *neither* adequate written description nor enablement of G-CSF agonist antibodies that bind to the *intra*cellular portion of G-CSF receptor. The specification does not provide an adequate written description of such antibodies, nor does it enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The art appreciates that it does not require undue experimentation to make agonist antibodies to a given receptor, including to the G-CSF receptor (see art rejections, below). However, as evidenced by that patents cited below, the art teaches that such antibodies bind to the *extracellular* domain of the receptor, which is that portion of the receptor to which G-CSF, the 'natural' agonist binds. The Examiner is unable to find any reports in the art of antibodies that act as receptor agonists, which bind to the *transmembrane or intracellular* portion of the receptor. As claim 34 specifically recites that the claimed antibodies bind to the extracellular portion, the Examiner concludes that applicants intend claims 31-33, 37, 38, 40 and 45 to specifically encompass antibodies that do *not* bind to the extracellular domain, i.e. bind to the transmembrane or intracellular domains of the receptor. As the art does not recognize that such antibodies would have the required function, and as the specification provides neither any written

description of such antibodies, nor any guidance or working examples of such, the Examiner concludes that the written description in the specification is not adequate to support such claims, and further, that undue experimentation would be required to practice such an invention in a manner commensurate in scope with the claims. Deletion of claim 34, as being not further limiting, or alternatively specification in the independent claims that the antibody binds to the extracellular domain would be remedial.

Claim 38 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fragments of antibodies that bind bivalently, does not reasonably provide enablement for monovalent fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Dimerization of G-CSF receptor is required for activation and signaling to occur. In fact, the specification as filed teaches at page 3, that "Homodimerization of the G-CSF receptor has been shown to be essential for signal transduction (We11s, J. A., and Vos, A. M., Annu. Rev. Biochem.,1996,65: 609)." U.S. Patent Number 5,506,107 (Cunningham et al.) teaches at column 24 that "monovalent antibodies, which only bind to one receptor molecule, are useful as antagonists." Accordingly, those species recited in claim 38 that are monovalent would be expected, in view of the specification and the art, not to be agonist antibodies. The specification provides no guidance or working examples, of how to make monovalent agonist antibodies, nor how to use monovalent antagonist antibodies in a fashion that would result in agonist activity. Accordingly, in view of the specification and the art, the Examiner concludes that it would require undue experimentation to practice the invention in a manner commensurate in scope with claim 38.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 31-38, 40, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Cunningham et al., US Patent No. 5,506,107.

Cunningham et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56. At columns 23-24, Cunningham et al. discuss agonist antibodies to the growth hormone receptor, and state that such antibodies may be raised by immunizing animals against growth hormone (and presumably screening the resultant antibodies for agonist properties). Also at columns 23-24, Cunningham et al. disclose such antibodies to be monoclonal, chimeric, or CDR grafted, and compositions comprising such antibodies. The screening methods for identification of agonist antibodies are disclosed at columns 36-39. Thus, Cunningham discloses the desirability of obtaining agonists of the G-CSF receptor, and further discloses methods of obtaining agonist antibodies consistent with the claims. Accordingly, Cunningham et al. fairly place the claimed invention in the hands of the public.

Claims 31-38, 40, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al., US Patent No. 6,342,220.

Adams et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56. Fragment and single chain antibodies are discussed at column 18. Methods of making the antibodies are disclosed at column 25. Thus, Adams discloses the desirability of obtaining agonists of the G-CSF receptor, and further

discloses methods of obtaining agonist antibodies consistent with the claims. Accordingly, Adams et al. fairly place the claimed invention in the hands of the public.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner